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SWITZER, JULIET CAROLINE	
ART UNIT	**PAPER NUMBER**
1634	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/803,648	LIEW, CHOONG-CHIN	
	Examiner	Art Unit	
	Juliet C. Switzer	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 4-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 4 is confusing because the final portion of the claim states that "a difference in the expression level of the gene in said test subject sample relative to said control subject blood is indicative of expression of said gene in said test subject." However, it is not clear how a difference between two values indicates expression in a first (i.e. the sample). For example, if the detection level in the test subject sample is zero, but there is expression in the control subject, there would be a difference between expression in the two samples, but this difference would not indicate the expression of the gene in the test sample. Claims 6-10 are also indefinite in view of this recitation since they depend from claim 4.

Claim 5 is indefinite over the recitation "liver tissue-specific gene" because it is not clear what it means to be a tissue specific gene in the context of the claimed invention, since the claims require the detection of a gene in blood, which is not liver tissue. The specification teaches provides a list of 1800 genes that were identified in a whole blood sample, and provides a table indicating that some of these genes have previously been detected in liver tissue as well. The specification further teaches that "Most of the cell or tissue specific genes are detectable in blood cells by RT-PCR analysis." Thus the specification teaches that these genes are not in fact

"tissue-specific," since they can also be detected in blood. It is not clear, therefore, in light of applicant's disclosure, which genes can be actually considered "tissue-specific" or what it means for a gene to be considered "tissue-specific." For example, it is not clear how many different tissues a gene can be detected in an still be considered to be "liver tissue-specific." Does the limitation require the detection of a gene that is expressed only in blood and liver tissue? Does the limitation require the detection of a gene that is expressed in blood an liver tissue, but could also be expressed in other tissues, provided it is not expressed in all tissues? There is no way to identify a gene as being "liver tissue-specific" and so the metes and bounds of this claim are unclear. Further, turning to the specification for guidance in understanding this phrase, it is noted that the specification describes the genes in Table 2 as demonstrating "the expression of known genes of specific tissue in blood cells" (i.e. tissue-specific genes) yet many of these genes were detected in all tissues listed (see for example 23 kD highly basic protein, p. 18 of specification) and this list also includes ubiquitious genes such GAPD (also known as GADPH, an essential enzyme for carbohydrate metabolism; p. 54). Thus, in light of the lack of definition of this term, and the fact that the claims require the detected gene be expressed in blood and liver both, the meaning of "liver-tissue specific gene" is indefinite.

In claim 6, the limitation "said RNA" lacks proper antecedent basis in claim 4. Since claim 6 refers to each of claims 1, 2, 3, and 4 in the alternative, proper antecedent basis for "said RNA" must be present in each of the independent claims.

In claim 7, the limitation "said ESTs" in line 1 of the claims lacks proper antecedent basis in claims 1, 2, 3, and 4. Claims 1 and 2 refer to singular "EST" but not more than one EST (at least it is not clear from the use of the abbreviation in claims 1 and 2 that the intention is plural

EST, given that the later claim specifically indicates the plural with an "s" after the acronym). Claims 3 and 4 do not provide any basis for this limitation.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Jiang et al. (British Journal of Cancer (1997) 75(6)928-933).

Jiang et al. teach the detection and quantification of alphafetoprotein (AFP) mRNA in a blood sample using a method which included production of cDNA and subsequent amplification by PCR (p. 929-930). Jiang et al. detect AFP mRNA via production of a cDNA (which is also an EST) from a blood sample using reverse transcription. AFP is a gene that is expressed in liver tissue.

Thus, regarding claim 1, Jiang et al. teach method of detecting the expression of a gene in a blood sample, said method comprising the step of detecting in RNA, cDNA or EST from a blood sample, the presence of an RNA, cDNA, or EST complementary to a gene expressed in liver tissue, wherein the detection of said RNA, cDNA or EST is indicative of the expression of said gene in said blood sample.

Regarding claims 2 and 4, Jiang et al. teach the comparison of levels of AFP mRNA among a variety of different types of patients, any of which can be labeled "sample" and

"control." Jiang et al. observe different levels of difference among different types of patients (see discussion p. 931). The determination that there was AFP mRNA in one blood sample but not another is a quantification and comparison which falls within the limitations of this claim.

Regarding claims 3 and 4, Jiang et al. produce PCR amplificiton products using gene specific primers to the AFP gene (p. 930).

Regarding claim 5, AFP is a "liver-tissue specific gene" insofar as this means that AFP is expressed in liver tissue.

Regarding claim 6, the simple detection of the presence or absence of a molecule in the sample (here by amplification of cDNA) is in fact a means of quantification in that the determination of the presence or absence provides a zero or non-zero value. Furthermore, however, it is noted that independent claims 1 and 2 both recite the detection of RNA, cDNA or EST complementary to a gene expressed in liver tissue, and claim 6 does not require that the detection is of RNA. Therefore, for claims 1 and 2, if the claim is read to require the option cDNA or EST, the limitation of claim 6 is not required since it would not limit either of these options, and since the claim does not include a statement that requires the detection of RNA in particular. Even if the claim did require RNA and quantification of RNA, as it appears applicant may intend, Jiang et al. meet this limitation, as discussed previously in this paragraph.

Claim 7 is anticipated by Jiang et al. because Jiang et al. meet all of the limitations of claims 1 and 2 as they refer to cDNA and though claim 7 further limits how the EST are generated, it does not require that the detection in claims 1 or 2 are of EST and so, claim 7 in its entirety is read, the limitation of claim 7 applies only to the embodiments of claims 1 and 2

wherein the detection is of cDNA. Since Jiang et al. can also to meets the requirement of detection of mRNA and of an EST, Jiang et al. anticipates claim 7.

With regard to claim 9, neither the specification nor the claims provide a definition of how much blood is in a "drop," and so, any size blood sample is considered to be a drop of blood.

With regard to claim 10, Jiang et al. test blood from a human.

5. Claims 1-10 are rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al. (British Journal of Cancer (1997) 76(5)628-633).

Wong et al. teach the detection and quantification of alphafetoprotein (AFP) mRNA and albumin mRNA in a blood sample using a method which included production of cDNA and subsequent amplification by PCR (p. 629-630). Wong et al. detect AFP mRNA via production of a cDNA (which is also an EST) from a blood sample using reverse transcription. AFP and albumin are both genes that is expressed in liver tissue.

Thus, regarding claim 1, Wong et al. teach method of detecting the expression of a gene in a blood sample, said method comprising the step of detecting in RNA, cDNA or EST from a blood sample, the presence of an RNA, cDNA, or EST complementary to a gene expressed in liver tissue, wherein the detection of said RNA, cDNA or EST is indicative of the expression of said gene in said blood sample.

Regarding claims 2 and 4, Wong et al. teach the comparison of levels of AFP and albumin mRNA among patients with HCC and normal subjects, either of which can be labeled "sample" and "control." Wong et al. observe different levels of difference among different types of patients (see discussion p. 630-631).

Regarding claims 3 and 4, Wong et al. produce PCR amplification products using gene specific primers to the AFP gene and to the albumin gene (p. 930).

Regarding claim 5, AFP is a "liver-tissue specific gene" insofar as this means that albumin and AFP are expressed in liver tissue.

Regarding claim 6, Wong et al. teach quantification of the RNA in the samples by comparison to a calibration curve (p. 630-631). Furthermore, however, it is noted that independent claims 1 and 2 both recite the detection of RNA, cDNA or EST complementary to a gene expressed in liver tissue, and claim 6 does not require that the detection is of RNA. Therefore, for claims 1 and 2, if the claim is read to require the option cDNA or EST, the limitation of claim 6 is not required since it would not limit either of these options, and since the claim does not include a statement that requires the detection of RNA in particular. Even if the claim did require RNA and quantification of RNA, as it appears applicant may intend, Wong et al. meet this limitation, as discussed previously in this paragraph.

Regarding claim 7, Wong et al. random primers followed by gene specific primers to produce EST that represent the target genes. Further, it is noted that though claim 7 further limits how the EST are generated, it does not require that the detection in claims 1 or 2 are of EST and so, claim 7 in its entirety is read, the limitation of claim 7 applies only to the embodiments of claims 1 and 2 wherein the detection is of cDNA.

With regard to claim 9, neither the specification nor the claims provide a definition of how much blood is in a "drop," and so, any size blood sample is considered to be a drop of blood.

With regard to claim 10, Wong et al. test blood from a human.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Nature of the invention

Claims 1 and 3 set forth methods for detecting the expression of a gene expressed in liver tissue in a blood sample based on detecting in RNA, cDNA or EST from a blood sample a molecule complementary to a gene expressed in liver tissue. The claims are non-specific as to any further use for the claimed invention, but turning to the specification to understand a potential use for the invention (i.e. to meet the 112 1st requirement for a disclosure of how to both make and use an invention), applicant suggests that the disclosed invention relates to using genetic information in blood "for the diagnosis, prognosis and monitoring of genetic and infectious disease in the human body (p. 1)." The nature of the invention, for using the invention, relies on the knowledge that genes expressed in the liver, which are also expressed in the blood have some diagnostic, prognostic or monitoring value. Claims 5-10 depend from claims 1 and 3 in the alternative and are included in this rejection insofar as they depend from the independent claims.

Claims 2 and 4 set forth methods for detecting expression of a gene which is expressed in liver tissue in a blood sample. Both of these claims set forth steps where a comparison between levels of expression in two samples (a test and a control sample) occurs and the claims set forth that a difference between the two samples "indicates a difference in the expression of said gene encoding said RNA, cDNA or EST in said sample (claim 2)" or "is indicative of expression of said gene in said test subject (claim 4)." Both of these claims have been rejected in this office action because they are indefinite. Nonetheless, it is clear that the nature of the invention suggests that a gene which is expressed in liver tissue can be detected as being expressed in blood, and further the nature of the invention suggests that a difference between samples can be detected, and that this difference may indicate something about gene expression. Further, like claims 1 and 4, the turning to the specification for guidance as to "how to use" the claimed invention, the specification suggests that methods for detecting gene expression in light of the disclosure might have diagnostic or prognostic value. Claims 5-10 depend from claims 2 or 4 in the alternative and are included in this rejection insofar as they depend from the independent claims.

Claim 5 further requires that the gene is a "liver tissue specific gene." This claim is also rejected as being indefinite in this office action, as the meaning of this phrase is unclear since the gene must be expressed in at least blood and liver tissues. However, this claim is discussed in this rejection in the interest of compact prosecution. The nature of the invention for this claim, no matter which independent claim is chosen for the context of the claim, requires the knowledge of genes that are "liver tissue-specific genes" whose expression can also be detected in the blood.

Scope of the claims

The claims are broad in scope with regard to the fact that the test genes are entirely unidentified. However, they are limited in that they must be genes that are expressed in both blood and liver tissue of a subject. Further, regarding claims 2 and 4, that one must be able to detect the differential expression of these genes between two subjects. Claim 5 requires that the gene must be a "liver tissue-specific gene." The claims are also extremely broad because they require only the comparison of a gene expression in a single individual's blood to that of another single individual, and the claims conclude that a difference in gene expression among these two individuals will be indicative of difference in expression between two samples. The claims are extremely broad with regard to how to apply the claimed invention (i.e. how to use the methods) since other than reciting the general purpose of detecting expression of difference in expression of a gene which is expressed in liver tissue in a blood sample, the claims do not limit the methods to any particular use.

Teachings in the Specification/Examples

The specification teaches the production of cDNA libraries from fetal heart, adult heart, liver, brain, prostate, and whole blood (p. 11, example 1). No results are given from this example.

Example 2 (p. 11) teaches the random partial sequencing of cDNA clones from the blood cell library, and categorizing of the genes into cellular functions. No results are given from this example.

Example 3 (p. 11-12) teaches screening of cDNA probes from transcripts of non-blood tissues to identify transcripts that were expressed only in blood. No results are given from this example.

Example 4 (p. 12) teaches RNA extracted from human tissue was subjected to RT-PCR for amplification of cardiac beta-myosin heavy chain gene (βMyHC), amyloid precursor protein (APP), and adenomatous polyposis-coli protein (APC) gene. Example 5 teaches that these three genes, which were previously thought to have tissue specific expression were detected in whole blood samples (p. 12-13). These genes are not taught to be expressed in liver tissue, nor are they taught to be "liver tissue-specific." Thus, these examples are not within the scope of this invention. Likewise, example 6 considers genes, which are not "liver tissue-specific" genes, nor are they expressed in liver tissue. Example 6 further provides discussion of additional genes that are not disclosed as expressed in liver tissue or being liver specific genes. Thus, these examples are not within the scope of this invention. Example 6 further demonstrates that the housekeeping gene glyceraldehyde dehydrogenase is not differentially expressed in the blood of disease vs. normal subjects. The specification teaches that this gene is highly expressed in all cells, and thus, this gene falls within the scope of genes that are expressed in liver. This gene would be considered within the scope of the genes recited in the claimed invention, as it would be expected to be expressed in liver tissue and blood tissue. Notably, no difference in expression was detected from two individuals.

The specification teaches in Example 7, that more than 95% of the clones identified in a human blood cell library are identical between blood and other tissue samples (p. 15). The specification teaches that of 20,000 seqeunced EST's from blood cell cDNA library, 17.6% appeared to be novel against GenBank, and others were known. In example 8, beginning on page 16, applicant provides in Table 2 a list of 1800 genes that were detected in a blood cell cDNA library and compares them with EST that were derived from human brain, heart, lung, and

kidney (beginning on p. 18). The specification teaches on page 142 that the comparisons presented in Table 2 are to previously identified tissue-specific genes determined using the GenBank of the National Centre of Biotechnology Information Database. The genes presented in table 2 are thus discussed as being "tissue specific," yet many of these genes appeared in all tissues discussed in the table, and many more in multiple tissues. Each of these genes was detected by Applicant in the blood libraries that were screened by applicant.

The specification is silent as to which of these genes are "tissue-specific" for liver tissue- in view of an interpretation that this would require that the gene is expressed only in liver tissue and blood, or even under any other definition. Further, the specification does not provide any guidance as to which of these genes might be identified as differentially expressed between control and test populations. The specification does not provide any guidance with regard to any particular gene that is disclosed as having been found in a blood library and a liver library as to how one might use the particular nucleic acids in any type of assay, for example, there is no demonstration that genes expressed in the liver and in blood are useful for the detection of any possible disease.

State of the Prior Art and Level of Unpredictablity

At the time the invention was made, it was known that expressed genes in whole blood could be detected as being differentially expressed and indicative of some diseases. For example, Wong et al. (cited in this office action) provide discussion of the detection of AFP and albumin, two genes that are expressed in liver tissue, in blood as an indicator of HCC. Regarding albumin in particular, Wong et al. teach the detection of this transcript in normal control patients and in cancer patients and establish a "threshold" level of expression that might

indicate HCC. So, some specific examples of assays within the scope of the claimed invention were known, as discussed in the prior art rejections herein. In each of these cases, for a change in expression to be considered meaningful, work was carried out to identify the marker gene and establish a statistically significant relationship between the disease phenotype and the differential expression. This is a highly unpredictable venture. Since one cannot know a priori which genes would be differentially expressed in blood of two groups at sufficient amounts to differentiate them.

Further, the claims of the instant application set forth the comparison of the gene expression between a "sample" and a "sample control" which encompasses the comparison of expression between as few as two individuals. Neither the specificaiton nor the claims, for any individual gene or for all genes in general, set forth a threshold of difference between two individuals that would be sufficient to conclude that the difference in gene expression between a healthy individual and any control individual is indicates a difference of expression that is biologically relevant or indicates that the gene is expressed in a subject. Turning to the specification to understand a potential use for the invention (i.e. to meet the 112 1st requirement for a disclosure of how to make and use an invention), applicant suggests that the disclosed invention relates to using genetic information in blood "for the diagnosis, prognosis and monitoring of genetic and infectious disease in the human body (p. 1)." It is highly unpredictable, however, what gene that is expressed in the blood and in liver tissue, an further, what liver tissue specific gene, would provide useful gene expression data when compared to another individual. Because the claims encompass any level of altered gene expression, it is relevant to point out that the post-filing art of Cheung et al (2003) teaches that there is natural

variation in gene expression among different individuals. The reference teaches an assessment of natural variation of gene expression in lymphoblastoid cells in humans, and analyzes the variation of expression data among individuals and within individuals (replicates) (p.422, last paragraph; Fig 1). The data indicates that, for example, expression of ACTG2 in 35 individuals varied by a factor of 17; and that in expression of the 40 genes with the highest variance ratios, the highest and lowest values differed by a factor of 2.4 or greater (Fig 3). It is thus unpredictable as to whether or not any level of altered gene expression is indicative of a disease.

Further, even when comparing populations, the unpredictability of correlating gene expression level to any phenotypic quality is taught in the post-filing art of Wu (2001). Wu teaches that gene expression data, such as microarray data, must be interpreted in the context of other biological knowledge, involving various types of 'post genomics' informatics, including gene networks, gene pathways, and gene ontologies (p.53, left col.). The reference indicates that many factors may be influential to the outcome of data analysis, and teaches that expression data can be interpreted in many ways. The conclusions that can be drawn from a given set of data depend heavily on the particular choice of data analysis. Much of the data analysis depends on such low-level considerations as normalization and such basic assumptions as normality (p.63 - Discussion). The art of Newton et al (2001) further teaches the difficulty in applying gene expression results. Newton et al teaches that a basic statistical problem is determining when the measured differential expression is likely to reflect a real biological shift in gene expression, and replication of data is critical to validation (p.38, third full paragraph).

Quantity of Experimentation

The instant specification does not provide enabling support for the practice of a single embodiment within the claimed invention. The specificaiton demonstrates the expression of a number of genes which were previously thought to be "tissue-specific" in human blood samples. However, the specificaiton does not establish a reliable statistical relationship between any of these and any particular use, other than for the detection of the expression of the genes themselves. The most experimental discussion of a gene that would be expected to be expressed in liver, is in example 6 regarding GADH. However, regarding claims 2 and 4, there is no showing that any biologically relevant difference in expression between two individuals or populations is present. For any of the genes mentioned in the specification, or any other gene that is expressed in liver, an extensive amount of work would be requried to practice the claimed invention. Table 2 provides a hundreds of genes that are expressed in blood and liver tissue. The specification does not demonstrate that any of these can be detected in the blood for any biologically relevant use, and further, the specification does not teach that any of these can have expression that is detectable at different levels among individuals or populations. The specificiaton does not associate any of these with disease that can be detected based on differential expression of the gene in blood of a patient with a disease. To practice the claimed invention for even these two examples, one would have to undertake substantial experimentaiton to determine that a predictive relationship exists, and what level of difference is necessary to be considered as useful within the uses of the claimed invention suggested by the instant specificaiton.

Regarding claims 1 and 3, and claims 6-10 insofar as they depend from claims 1 and 3, it is clear from the teachings of the specification (Table 2) that there are many genes which were

detected in human blood that have also been detected in expression libraries obtained from liver tissue. However, while this may satisfy the "how to make" portion of 112 1st paragraph, since one could follow the guidance in the specificaiton to detect any of these listed genes in blood of a human, it does not satisfy the "how to use" portion of 112 1st paragraph, since for the reasons outlined in this rejeciton, one would not know how to use such a method- that is, to what end the method would be useful, based on the teachings of the specification. Regarding claims 2 and 4, since the specificaiton does not provide any guidance as to which of the genes set forth in Table 2 might be differentially expressed among populations or even among individuals there is no guidance in the specification as to which of the thousands of genes listed in Table 2 might be useful in the claimed methods which require analysis of differential expression.

Conclusion

The identificaiton of gene differential expression/disease indication relationships is a highly unpredictable endavour, requiring extensive experimentaiton. Thus, in light of all of these factors considered in this rejection, namely, the nature of the invention, the scope of the claims, the lack of working examples and guidance in the specificition, and the unpredictable nature of the invention, it is concluded that it would require undue experimentation to pracitce the claimed invention.

8. Claims 2, 4 and 5-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejected claims set forth methods for detecting expression of a gene which is expressed in liver tissue in a blood sample. Both of these independent claims set forth steps where a comparison between levels of expression in two samples (a test and a control sample) occurs and the claims set forth that a difference between the two samples "indicates a difference in the expression of said gene encoding said RNA, cDNA or EST in said sample (claim 2)" or "is indicative of expression of said gene in said test subject (claim 4)." Both of these claims have been rejected in this office action because they are indefinite. Nonetheless, it is clear that the nature of the invention suggests that a gene which is expressed in liver tissue can be detected as being expressed in blood, and further the nature of the invention suggests that a difference between samples can be detected, and that this difference may indicate something about gene expression. Claims 5-10 depend from claims 2 or 4 in the alternative and are included in this rejection insofar as they depend from the independent claims.

Claim 5 further requires that the gene is a "liver tissue specific gene." This claim is also rejected as being indefinite in this office action, as the meaning of this phrase is unclear since the gene must be expressed in at least blood and liver tissues. However, this claim is discussed in this rejection in the interest of compact prosecution. The nature of the invention for this claim, no matter which independent claim is chosen for the context of the claim, requires the knowledge of genes that are "liver tissue-specific genes" whose expression can also be detected in the blood.

The claims are broad in scope with regard to the fact that the test genes are entirely unidentified. However, they are limited in that they must be genes that are expressed in both blood and liver tissue of a subject and that one must be able to detect the differential expression

of these genes between two subjects. Claim 5 requires that the gene must be a "liver tissue-specific gene."

The specification provides reference by "gene name" and a GenBank accession number for hundreds of genes that were identified by applicant as being expressed in the blood, and also provides summary of previously available information from the NCBI database as to the expression of these genes in liver tissue (Table 2). The specification does not provide any written description, from these hundreds of possible genes, as to which are differentially expressed in amounts detectable in the blood of individuals. There does not appear to be any structural or chemical feature of such genes that would make them readily identifiable. There are no examples of genes that meet the requirements of the instant claims given in the specification. There is no representative number of examples of genes that would function in the claimed assay. There is no description, of all of the genes listed in table 2 as to which might be determined as being "differentially expressed" among two individuals or two population.

Thus, the claims are rejected for lack of adequate written description.

Conclusion

9. No claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Juliet C Switzer whose telephone number is (571) 272-0753. The examiner can normally be reached on Monday, Tuesday, or Thursday, from 9:00 AM until 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's

supervisor, Ram Shukla can be reached by calling (571) 272-0735.

The fax phone numbers for the organization where this application or proceeding is assigned are (571) 273-8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)272-0507.

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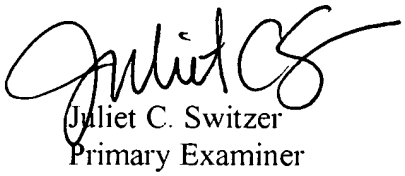

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